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Computational Models of Transcranial Direct Current Stimulation

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Abstract

During transcranial direct current stimulation (tDCS), controllable dose parameters are electrode number (typically 1 anode and 1 cathode), position, size, shape, and applied electric current. Because different electrode montages result in distinct brain current flow patterns across the brain, tDCS dose parameters can be adjusted, in an application-specific manner, to target or avoid specific brain regions. Though the tDCS electrode montage often follows basic rules of thumb (increased/decreased excitability "under" the anode/cathode electrode), computational forward models of brain current flow provide more accurate insight into detailed current flow patterns and, in some cases, can even challenge simplified electrode-placement assumptions. With the increased recognized value of computational forward models in informing tDCS montage design and interpretation of results, there have been recent advances in modeling tools and a greater proliferation of publications. In addition, the importance of customizing tDCS for potentially vulnerable populations (eg, skull defects, brain damage/stroke, and extremes of age) can be considered. Finally, computational models can be used to design new electrode montages, for example, to improve spatial targeting such as high-definition tDCS. Pending further validation and dissemination of modeling tools, computational forward models of neuromodulation will become standard tools to guide the optimization of clinical trials and electrotherapy.

Keywords

tDCS, transcranial electrical stimulation, computer model, forward model, FEM, current flow, electric field, current density

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Uses and Need for Computational Models of Noninvasive Neuromodulation

Transcranial electrical stimulation is a promising tool in cognitive neuroscience and neuropsychiatric therapy based on the growing evidence that delivery of current to specific brain regions can modulate excitability[1,2] and, in some cases, promote desirable plastic changes.[3,4] Of particular interest are neurostimulation modalities that are of low cost, portable, and simple to implement. Furthermore, stimulation should be delivered in a manner that is safe, well tolerated, and can be applied concurrently with neuropsychological testing or even moderate physical activity. Transcranial direct current stimulation (tDCS) has been gaining considerable interest because it possesses all these desired qualities.[5]

In contrast to pharmacotherapy, noninvasive electrotherapy offers the potential for both anatomically specific brain activation and complete temporal control since electricity is delivered at the desired dose instantly, and there is no electrical "residue" as the generated brain current disappears when stimulation is turned off. Thus, tDCS can be customized and individualized to specific brain targets in ways not possible with other interventions in order to optimize a particular rehabilitative outcome. Specifically, the dose of electrotherapy is readily adjustable by determining the number, shape, size, and location of electrodes (which determines spatial targeting) and selecting the stimulation waveform (which determines the nature and timing of neuromodulation). Indeed, a single programmable electrotherapy device can be simply configured to provide a diversity of dosages.

Though this flexibility underpins the utility of neuromodulation, the myriad of potential dosages (eg, stimulator settings and combinations of electrode placements) can lead to a great number of possibilities, thus making the optimal choice very difficult to readily ascertain. The essential issue in dose design is to relate each externally controlled dose with the associated brain regions targeted (and spared) by the resulting current flow and hence the desired clinical outcome. Computational forward models aim to provide precisely these answers to the first part of this question (Figure 1) and thus represent a critical tool in

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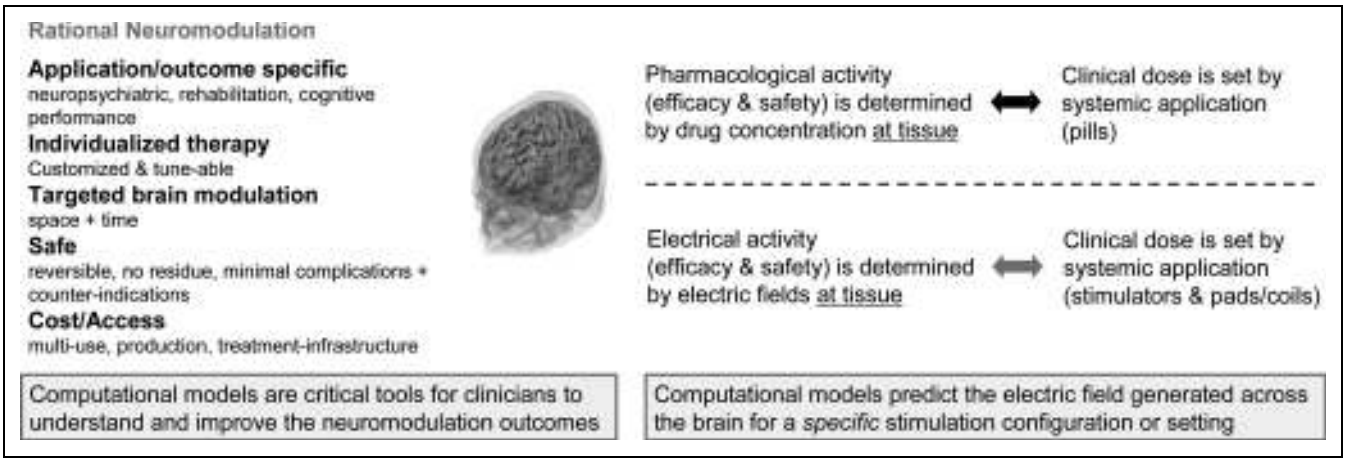

Figure 1. Role of computational models in rational electrotherapy. (Left) neuromodulation is a promising therapeutic modality as it affects the brain in a way not possible with other techniques and a high degree of individualized optimization. The goal of computational models is to assist clinicians in leveraging the power and flexibility of neuromodulation. (Right) All computational forward models are used to predict brain current flow during transcranial stimulation to guide clinical practice. As with pharmacotherapy, electrotherapy dose is controlled by the operator and leads to a complex pattern of internal current flow that is described by the model. In this way, the clinicians can apply computational models to determine which dose will activate (or avoid) the brain regions of interest.

the rational design, interpretation, and optimization of neuromodulation.

Methods for the Generation of Computational Forward Models of tDCS

Computational models of tDCS range in complexity from concentric sphere models to high-resolution models based on individual's magnetic resonance image (MRI). The appropriate level of modeling detail depends on the clinical question being asked (as well as the available computational resources). Whereas simple geometries (eg, spheres) may be solved analytically,[6] realistic geometries employ specialized software, as described below, including numerical solvers (namely finite element methods [FEM]). Regardless of complexity, all forward models share the primary outcome of correctly predicting brain current flow during transcranial stimulation to guide clinical therapeutic delivery.

For clinicians interested in using computational forward models to inform study design or interpretation several options are available: (1) a collaboration with a modeling group[6] or a company can allow for customized exploration of montage options; (2) Referencing existing published reports or databases (Table 1) for comparable montages (with careful consideration of the role of individual variation and other caveats presented in the next section; see also http://neuralengr.com/bonsai); (3) by utilizing a recently developed process where a desired brain target can be selected and the optimized stimulation electrode montage is proposed within seconds.[7] If tDCS continues to emerge as an effective tool in clinical treatment and cognitive neuroscience, and concurrent modeling studies emphasize the need for rational (and in cases of patient-specific) dose decisions, then it will become incumbent for clinical research teams to understand the applications (and limitations) of computational forward models, which motivates this section.

While the specific software applications used can vary across modeling groups, in general, the approach and work flow for model generation follow a similar pattern (Figure 2). The steps for generating high-resolution (anatomically specific) forward models of noninvasive neuromodulation are adapted from extensive prior work on computational modeling. These involve step 1—demarcation of individual tissue types (masks) from high-resolution anatomical data using a combination of automated and manual segmentation tools. It is worth noting that the respective contribution of the automated/manual interventions depends on (a) sophistication of the particular automated algorithm employed since they are usually not optimized for forward transcranial modeling[8] and (b) the need for identification of anomalies in suspect populations like skull defects, lesions, shunts, and so on. Consequently, as emphasized below, the number and precision of the individual masks obtained is pivotal for the generation of accurate 3-dimensional (3D) models in order to capture critical anatomical details that may influence current flow. Step 2—modeling of the exact physical properties of the electrodes (eg, shape and size) and precise placement within the segmented image data (ie, along the skin mask outer surface). Step 3—generation of accurate meshes (with high-quality factor) from the tissue/electrode masks while preserving resolution of subject anatomical data. Step 4—resulting volumetric meshes are then imported into a commercial FE solver. Step 5—at this step, resistivity is assigned to each mask and the boundary conditions are imposed. The standard Laplacian equation is solved using appropriate numerical solver and tolerance settings.[7,9,10] Step 6—data are plotted as induced cortical electric field or current density maps.

Though each of the above steps is required for high-resolution modeling, there remains technical expertise and

Table 1. Synopsis of tDCS Computer Models: Summary of tDCS Forward Head Models[a]

Study	Masks	Electrode Montage	Additional Methods
Concentric sphere			
Miranda et al[10]	4 tissue models	4 montages	
Datta et al[7]	4	6 montages	
CAD rendered			
Wagner et al[9]	5	Healthy and stroke models with varied montages	
MRI derived			
Oostendorp et al[28]	5	C3 – SO montage	Anisotropic conductivities for skull and white matter. Model derived from Wolters et al
Datta et al[26]	4	C3-SO and high-definition (HD) montages.	High-resolution with gyri-sulci topography
Suh et al[13]	5	C3-C4 montage using point source stimulation electrodes	Anisotropic conductivity for white matter
Datta et al[7]	4	Tissue temperature increases for C3-SO montage and HD montage	
Sadleir[37]	11	F3-SO and F4-SO montage and comparison to reported clinical outcomes in literature	
Datta et al[34]	4	Effect of skull defects and skull plates for C3-SO and O1-SO montages	
Bikson et al[22]	7	C3-SO and C3 contralateral mastoid	Effect of "return electrode" position and size
Salvador et al[14]	5	C3-SO montage	High-resolution gyri-sulci model
Parazzini et al[15]	26 unique tissue types	Analysis of current flow through cortical, subcortical, and brain stem regions for C3-SO montage	Model derived from virtual family open source database
Mendonca et al[35]	8	C3 extracephalic, SO extracephalic and C3-SO montages	Correlation of clinical effects in a fibromyalgia study with model predictions
Halko et al[17]	7	Oz-Cz montage	Patient-specific visual stroke model of a hemianopia patient undergoing tDCS; correlation of high-resolution current flow model predictions with fMRI
Datta et al[8]	8	Retrospective analysis comparing experimental outcome with model predictions. LFC-RS, LFC-contralateral mastoid, LFC-SO, and RFC-LS	Patient-specific left hemisphere stroke model of a tDCS responder
Turkeltaub et al[6]	8	Analysis of left pTC and right pTC montage in dyslexia study	
Bonsai—Model Solution Analyzer neuralengr.com/bonsai	6-8	Healthy and stroke model with varied montages	Online database of solved patient-specific head models. Overlaid views of 2D MRI scans and model solutions.

Abbreviations: C3, C4, F3, F4, O1, Oz, Cz correspond to 10/20 EEG system; SO, contralateral supraorbital; LFC, left frontal cortex; RFC, right frontal cortex; RS, right shoulder; LS, left shoulder; pTC, posterior temporal cortex; EEG, electroencephalograph; fMRI, functional magnetic resonance imaging; 2d, 2-dimensional; tDCS, transcranial direct current stimulation.

[a] Head models have progressed from being spherical based to being MRI derived. The most recent ones have employed patient-specific models. The second, third, and fourth columns list number of tissue types, the montage used, and particular model specifics, respectively.

hence variation in protocols across groups and publications. These variations are relevant to clinical practice only in the sense that they change predictions in current flow that may eventually effect dose decisions. The sources and impact of these variations is addressed in the next section.

The precise pattern of current flow through the brain is determined not only by the stimulation dose (montage; the positions of the electrodes) but also by the underlying anatomy and tissue properties. In predicting brain current flow using computational models, it is therefore important to precisely model both the stimulation condition itself and the relevant anatomy upon which it is delivered on an individual basis. Modeling electrode geometry (eg, pad shape and position) and stimulation intensity (eg, total current applied) is relatively straightforward. However, the representing tissue remains an area of ongoing technical development and is critical to establishing the clinical utility of these models. For example, cerebral spinal fluid (CSF) is highly conductive (a preferred "super highway" for current flow) such that the integrated details in CSF architecture profoundly shape current flow through adjacent brain regions (see supplementary figure in Datta et al[26]).

Initial models of transcranial current flow assumed simplified geometries such as concentric spheres that could be solved analytically[11,12] as well as numerically.[7,12] Such concentric sphere models are useful to address generic dose questions such

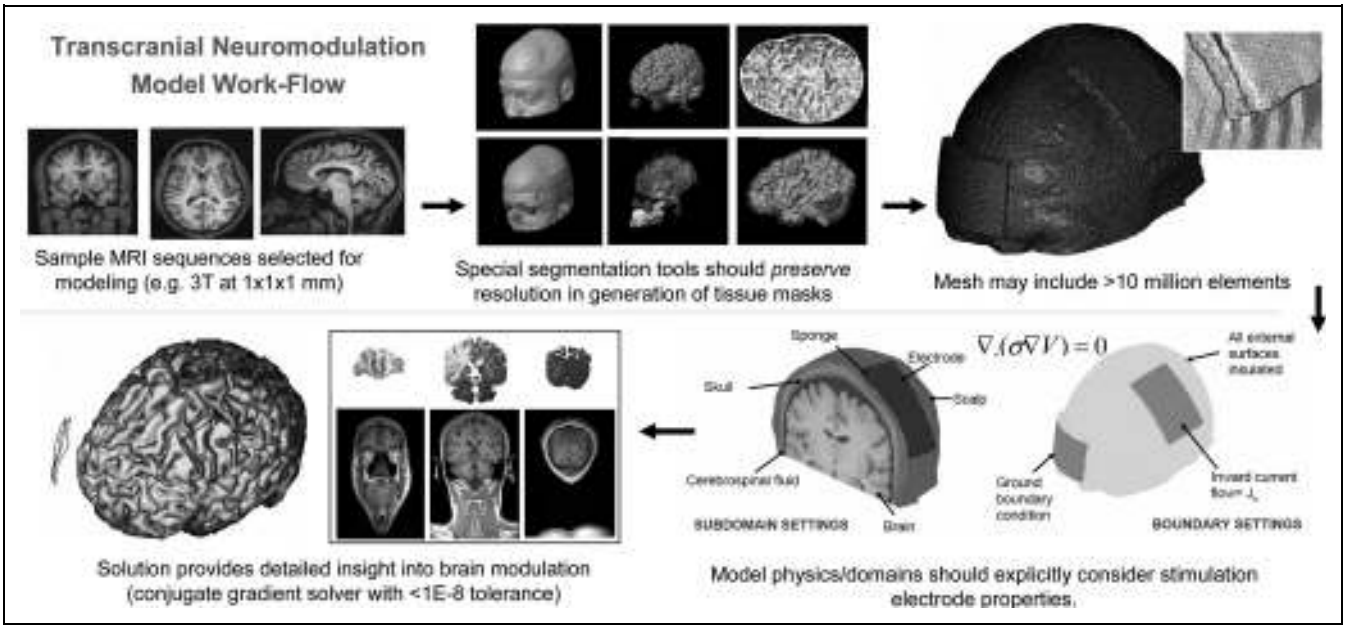

Figure 2. Imaging and computational work flow for the generation of high-resolution individualized models. Though the specific processes and software packages will vary across technical groups and applications, in each case the high-resolution modeling initiated with precise anatomical scans that allow demarcation of key tissues. Tissues with distinct resistivity are used to form "masks." These masks along with the representation of the physical electrodes are "meshed" to allow FEM calculations. The boundary conditions (generally simply reflecting how the electrodes are energized) and the governing equations (related to ohms law) are well established. The reproduction of the stimulation dose and the underlying anatomy thus allow for the prediction of resulting brain current. These current flow patterns are represented in a false-color map and analyzed through various postprocessing tools.

as the global role of interelectrode distance, electrode montage, or the relationship between electrode and brain current density, precisely because they exclude regional anatomical differences.[7,12] More realistic models started to include explicit representation of human anatomy.[9] Datta et al[26] published the first model of tDCS with gyri resolution, illustrating the importance of anatomical precision in determining complex brain current flow.[14] Addition of diffusion tensor imaging (DTI) incorporates anisotropic properties in the skull and the white matter regions[13] Fine resolution of gyri/sulci leads to current "hot spots" in the sulci, thereby reinforcing the need for high-resolution modeling.[14] An open-source head model comprising of several different tissue types was adapted to analyze current flow through cortical, subcortical, and brain stem structures.[15]

Recent studies have attempted to more directly link clinical outcomes and model predictions and thus validate model utility. Clinical evaluation was combined with model predictions to investigate the effects of different montages in clinical conditions such as fibromyalgia.[16] Recently, patient-specific models have been used to retrospectively analyze the therapeutic success of a given experimental stimulation montage[9] and compare model predictions with patterns of activation revealed by functional MRI (fMRI).[17]

Recent effort has been directed toward increasing the precision of tDCS models by enhancing model sophistication. However, it is important to note that increased model complexity does not necessarily equate with greater accuracy or clinical value.[18] Indeed, to meaningfully guide clinical utility attempts to enhance model precision must rationally balance detail (ie, complexity) and accuracy. (1) Beginning with high-resolution anatomical scans, the entire model work flow should preserve precision. Any human head model is limited by the precision and accuracy of tissue segmentation (ie, "masks") and of the assigned conductivity values. One hallmark of precision is that the cortical surface used in the final FEM solver should capture realistic sulci and gyri anatomy. (2) Simultaneously, a priori knowledge of tissue anatomy and factors known to influence current flow should be applied to further refine segmentation. Particularly critical are discontinuities not present in nature that result from limited scan resolution; notably both unnatural perforations in planar tissues (eg, ventricular architecture. discontinuities in CSF where brain contacts skull, misrepresented skull fissures) and microstructures (eg, incomplete or voxelized vessels) can produce significant deviations in predicted current flow. Moreover, because of the sensitivity of current flow to any conductivity boundary, increasingly detailed segmentation (eg, globe of the eye and related structures, glands, and deeper midbrain structures) without reliable reported human conductivity values in literature (especially at static frequency) may also lead to errors. Thus, addition of complexity without proper parameterization can evidently decrease prediction accuracy. An improper balance between these factors can introduce distortions in predicted brain current flow.

Finally, when clinicians are interpreting simulation predictions, it is important to recognize that the intensity of current flow in any specific brain region does not translate in any

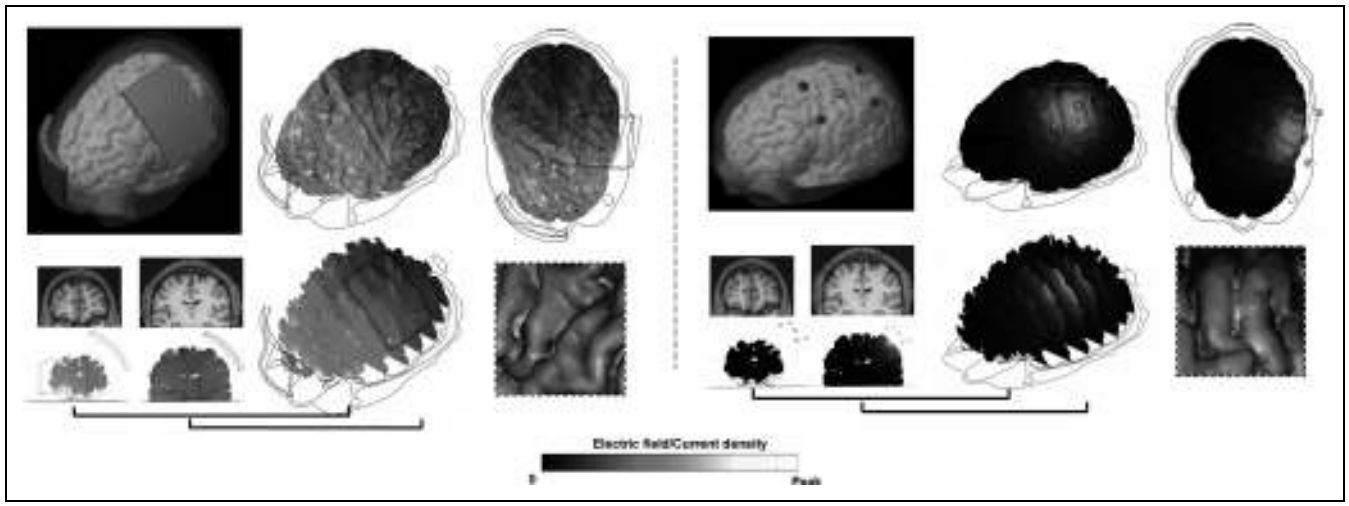

Figure 3. High-definition (HD) tDCS. Comparison of current density focality using the HD-tDCS 4 × 1-Ring deployment versus a convention "pad" tDCS montage. (Left) Some conventional tDCS montages can result in relatively diffuse and unfocal brain stimulation; in some cases, with peak currents between, not under, the electrodes (inset). (Right) In contrast, HD-tDCS ring stimulation results in highly targeted cortical area directly under the electrodes (see Datta et al[26]). tDCS indicates transcranial direct current stimulation.

simple (linear) manner to the degree of brain activation or modulation (even when considering current direction).[7,14] Moreover, recent neurophysiological studies indicate changes in ''excitability'' may not even be monotonic with stimulation dose and may in fact reverse depending on background activity. However, to a first approximation, it seems reasonable to predict that regions with more current flow are more likely to be ''effected'' by stimulation while regions with little or no current flow will be spared the direct effects of stimulation. As a first step to understand mechanism of action of tDCS, a relationship between model predicted regional current flow and changes in functional activation was recently demonstrated.[19] The central ''quasi-uniform'' assumption considers that if the electric field is uniform on the scale of a region (neuron) of interest, then ''excitability/neuromodulation'' may indeed be considered to change directly with the local electric field intensity[20] (see discussion in Datta et al[7] and Miranda et al[10]).

Future Directions

As computational models continue to evolve in sophistication, new methodologies like DTI have been included to investigate anisotropic tissue resistivity contributions to current flow inside the brain.[21] This section, however, addresses how clinicians can directly leverage existing models to improve patient outcomes of stimulation.

Retrospectively, computational models of tDCS provide a precise substrate to test mechanistic hypothesis about region-specific effects on cognition or behavior. In addition, computational models have contributed to the design and validation of new tDCS montages. This includes variations in the conventional 2-electrode pad montage[22] (1 anode and 1 cathode) but also the introduction of new therapeutic approaches.[23,24]

For example, high-definition tDCS (HD-tDCS) is a new modification of tDCS and uses arrays of specialized compact scalp electrodes to deliver current with no skin irritation and minimal discomfort.[25] Using a computational model, the ''4 × 1'' HD-tDCS deployment—where a central ''active'' electrode is surrounded by a ring of 4 ''return'' electrodes—was predicted to allow unprecedented targeting of cortical regions with DC neuromodulation[26] (Figure 3). Subsequent to these model predictions, clinical studies to validate the focality and efficacy of 4x1 HD-tDCS are ongoing. Still more sophisticated HD deployments, using up to 64 electrodes to focus current to targeted brain structures, have been proposed.[27]

Participant-to-participant variability is expected with any clinical intervention and neuromodulation, and especially tDCS allows for the potential individual customization of montage to normalize outcomes—specifically by controlling the amount of current delivered to a region/regions of interest. The inverse question is given the same montage is used across participants, how different is the resulting brain current flow in each patient? Notably, most published forward modeling studies and analysis are in fact published as ''case reports'' with predictions only on a single head.[3,28] For a given electrode montage and stimulation dose, the sensitivity of global brain current to normal variation in anatomy (including across ages, gender) is poorly understood; however, high-resolution modeling suggests gyri-specific dispersion of current flow, which could potentially account for individual variability.[14,29-31] More generally, gross differences in tissue dimensions, notably skull thickness, are expected to influence current flow.

There is increasing interest in the use of neuromodulation at the extremes of age, including for aging-related disorders, and in pediatric populations for indications including autism and epilepsy treatment.[32] However, because the intensity of brain current generated during stimulation depends on *both* the tDCS

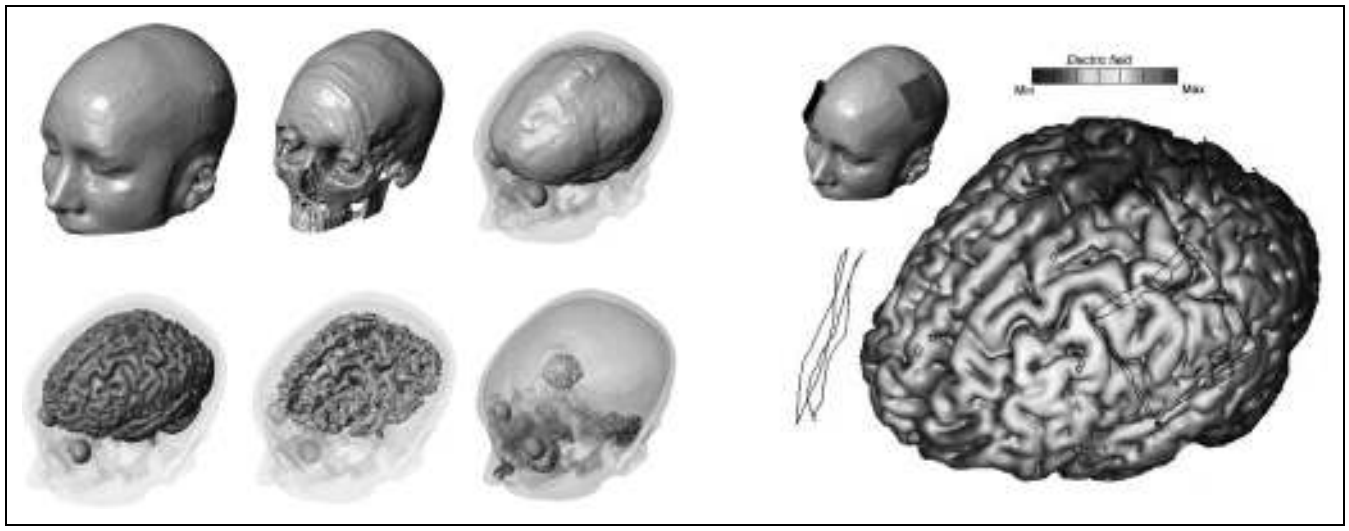

Figure 4. Individualized head model of a 12-year-old, showing segmentation masks and induced current flow for motor cortex tDCS.

dose (montage and current intensity) and the underlying brain anatomy, the same dose applied may produce different brain current in young or elderly participants.[33] For example, it would not be prudent to adjust stimulation dose for children through an arbitrary rule of thumb (eg, reduce electrode size and current intensity by the ratio of head diameter). Computational forward models provide direct insight into the relation between external tDCS dose and resulting brain current and thus can inform dose design in such cases. Figure 4 shows an example of a model of tDCS in a 12-year-old. Both the peak and spatial distribution of current in the brain is altered compared to the typical adult case. Though questions remain about the impact of gross anatomical (eg, age, gender, etc) differences in altering generated brain current flow during neuromodulation, computational "forward" models provide direct insight into this question and may ultimately be used to rationally adjust stimulation dose.

In more extreme cases, modeling efforts specifically addressed the role of individual anatomical pathology, such as skull defects[34] or brain lesions.[8] For example, tDCS has been shown to modulate cognitive, linguistic, and motor performance in both healthy and neurologically impaired individuals with results supporting the feasibility of leveraging interactions between stimulation-induced neuromodulation and task execution.[17,22,35] However, while numerous reports have been published in recent years demonstrating the effects of tDCS upon task performance, there remain fundamental questions about the optimal design of electrode configuration, especially around lesioned tissue.[24] Several modeling studies have demonstrated the profound influence of stroke-related brain lesions on resulting brain current produced by tDCS.[9,10,26] These studies demonstrate the potentially profound influence of lesions and skull defects on resulting current flow.

At the same time, there is clinical interest in the application of tDCS during rehabilitation of patients with brain lesions or skull defects (ie, with or without skull plates) such as traumatic brain injury or patients undergoing neurosurgery. As some of the neurological sequelae are presumably consequences of disrupted cortical activity following the traumatic event, the use tDCS to deliver current to both damaged and compensatory regions in such circumstances can be a useful tool to reactivate and restore activity in essential neural networks associated with cognitive or motor processing.[36] Modeling studies can provide insight into how skull defects and skull plates would affect current flow through the brain and how to modify tDCS dose and/or electrode locations in such cases (Figure 5, adapted from Datta et al[34]). It is precisely because these studies have shown the importance of specific defect/lesion details that individual analysis of tDCS-induced current flow seems warranted in such cases.

Conclusion

While numerous published reports have demonstrated the beneficial effects of tDCS upon task performance, fundamental questions remain regarding the optimal electrode montage. Moreover, it is expected that individual anatomical differences, in the extreme case manifest as skull defects, and lesioned brain tissue, will influence current flow and should therefore be considered (and perhaps leveraged) in the optimization of neuromodulation therapies. Computational models can underpin the design and evaluation of more effective tDCS montages and thus contribute to the validation of tDCS.

Declaration of Conflicting Interests

The authors declared a potential conflict of interest with respect to the research, authorship, and/or publication of this article: Dr Datta is co-founder of Soterix Medical. The City University of New York has patent applications in Dr Datta's name on brain stimulation. The City University of New York has patent applications in Dr Bikson's name on brain stimulation. Dr Bikson is co-founder of Soterix Medical.

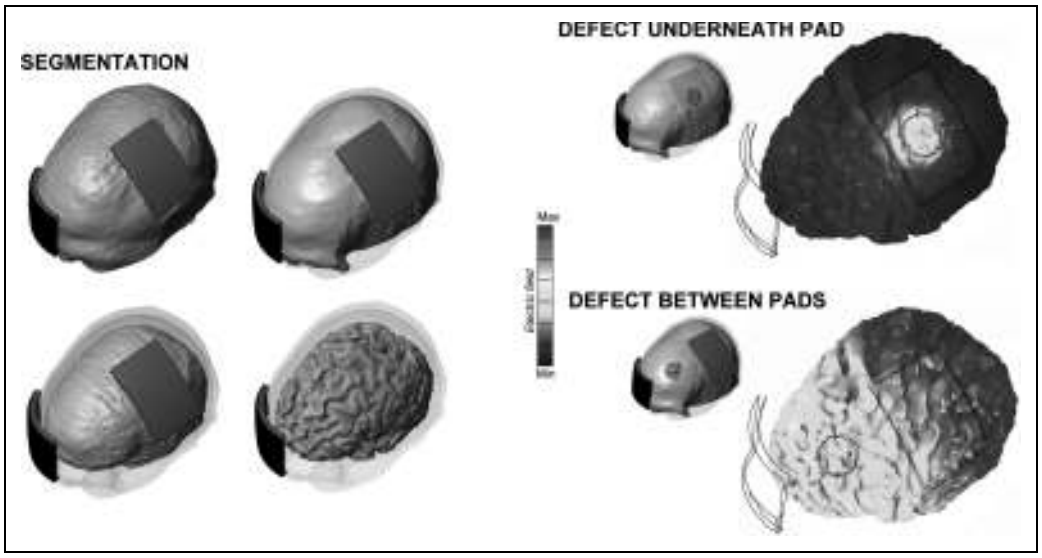

Figure 5. Computational model of current flow in participants with skull defects/plates. A defect in skull tissue, which is the most resistive tissue in the head, would hypothetically affect current flow in the underlying brain regions. Furthermore, the exact location of the defect (under/between the stimulation pads) in combination with the "material" filling up the defect with the stimulation montage employed will influence the induced current flow. Sample segmentation masks are shown on the left side. A small defect under the anode pad (top right) leads to current flow in the cortex restricted to directly under the defect (avoiding the intermediate regions). A similar-sized defect placed between the pads (bottom right) does not significantly alter current flow patterns in comparison with a healthy head with no defects.[25]

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